REMARKS

FORMAL MATTERS

Claims 28-30, 36-37 and 41-46 are pending in the instant application. The amendments made herewith are fully supported by the as-filed specification.

Applicant has amended claim 1 to recite that the polypeptide comprises the amino acid sequence of SEQ ID NO:1. The polypeptide of SEQ ID NO:1 is expressly recited in the specification (*see, e.g.*, p. 29, Table 1).

Independent claims 37 and 44 have been amended to recite that the peptide fragment is between 40 and 66 amino acids in length. Support for these amendments can be found, for example, at least at page 2, lines 26-30; page 7, line 10; page 11, line 22; and original claim 18.

Accordingly, the present amendments do not introduce new matter.

Applicant notes the Examiner's acknowledgement of the election of Group VI. Applicant has cancelled claims 1-27 and 31-35 as drawn to a non-elected invention.

Applicant notes with appreciation that the drawing filed 2/18/00 has been approved.

The Examiner has objected to the oath or declaration for failing to identify the provisional application corresponding to the instant application. A new declaration identifying the application number and filing date of the instant application is filed herewith.

The Examiner has requested an amendment to the specification in order to add the Accession Number for hybridoma 5E11. Applicant is in the process of making a biological deposit according to the provisions of the Budapest Treaty, further to In re Lundak. Applicant will amend the specification upon receipt of an Accession Number.

As suggested by the Examiner, the dashed line on page 24, line 26 has been amended to read "pp. 155-194", and the underscore on page 24, line 28 has been removed.

The corresponding SEQ ID NOs have been added for the Figure under the Brief Description of the Drawings.

The Examiner has noted that the range "20-90" on page 11, line 22 does not provide support for claim 39, which recites a range of "20-72". The fragment range of 20-90 on Page 11,

line 22 has been deleted.

The Examiner has objected to claims 30, 43, and 46 because the limitation "acid phosphatase" is recited twice in the claims. The duplicate recitation of acid phosphatase in claims 30, 43 and 44 has been removed. Thus, this rejection is overcome.

Applicant acknowledges that claims 28-30, 36 and 41 are free of prior art. (*See* Office Action at page 10).

CLAIM REJECTIONS – §112, FIRST PARAGRAPH

ENABLEMENT

The Examiner has rejected claims 28-30 and 36-46 under 35 U.S.C. § 112, first paragraph, contending that the specification, while enabling for a method of inhibiting T cell response of a mammal sensitive to a protein allergen from bee venom comprising administering a substantially pure polypeptide comprising an amino acid sequence of SEQ ID NO:1, is not enabling for a method of inhibiting an immune reaction comprising administering a polypeptide that is at least 70% identical to the amino acid sequence of SEQ ID NO:1.

Claims 38-40 have been cancelled. Thus, this rejection, as it applies to these claims is moot and should be withdrawn. As noted, Applicant has amended independent claim 28 to remove the "at least 70% identical" limitation. Claim 28 as amended (and, thus, dependent claims 29, 30, and 36), now recites a substantially pure polypeptide comprising an amino acid sequence of SEQ ID NO:1. As conceded by the Examiner, the specification is enabling for such a claim. (*See* Office Action at page 3). Thus, the rejection as it applies to claims 28, 29, 30 and 36 is moot and should be withdrawn.

The Examiner also contends that the specification is not enabling for claims directed to *any* fragment of the amino acid sequence of SEQ ID NO:1, such as between 6-72, 20-72, 37-70, or 40-60 amino acids in length. (*See* Office Action at page 3). Independent claims 37 and 44 (and thus dependent claims 41-43 and 45-46) have been amended to require that the polypeptide fragment is between 40 and 66 amino acids in length. Applicant submits that the claims, as amended, relate to a discrete number of possible peptide fragments and that the specification sufficiently enables one of ordinary skill in the art to practice the invention as now claimed without undue experimentation. For example, the specification discloses Api m 6.04, a 73 amino

acid peptide (designated SEQ ID NO:4) and three long fragments of this peptide: Api m 6.01, a 67 amino acid peptide (designated SEQ ID NO:1), Api m 6.02, a 69 amino acid peptide (designated SEQ ID NO:2), and Api m 6.03, a 71 amino acid peptide (designated SEQ ID NO:3). *See, e.g.,* page 29 and FIG. 1 of the as-filed specification. Accordingly, the rejection should be withdrawn

Moreover, the Examiner also asserts that the skilled artisan would not be able to practice the invention without undue experimentation. In Wands, the Federal Circuit stated,

> [A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In re Wands, 858 F2d 731 (1988).

All of the techniques required to practice the claimed methods are described in the specification or are well-known to those skilled in the art as of the filing date. Peptide fragment generation is described in the specification at least at page 8, lines 12-29. It would be a matter of routine practice for one of ordinary skill in the art to generate a non-random library of peptide fragments between 40 and 66 amino acids in length when the amino acid sequence of the parent peptide (*e.g.*, the amino acid designated SEQ ID NO:1) is provided. Additionally, the specification teaches how to assay full length peptides or peptide fragments for the ability to alter or modulate cellular functions, such as modulating an immune response (*e.g.*, T-cell proliferation or IgE-mediated immune reactions). *See, e.g.*, Specification at page 8, lines 1-11; and page 10 line 28- page 11, line 18. Therefore, the claimed methods satisfy the Wands criteria set forth above, and are fully enabled by the specification.

WRITTEN DESCRIPTION

The Examiner has rejected claims 28-30 and 36-46 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor was in possession of the invention at the time the application was filed. Claims 38-40 have been cancelled. Thus, this rejection is moot with respect to these claims. Moreover, Applicant has herewith amended independent claim 28 to remove the "at least 70% identical" limitation. Claim 28 as amended (and thus dependent claims 29, 30, and 36) recites a substantially pure polypeptide comprising an amino acid sequence of SEQ ID NO:1. Because the amino acid sequence described by SEQ ID NO:1 is

disclosed on page 29, the specification clearly provides a written description of Claim 28 and dependent claims 29, 30 and 36 as amended. Thus the rejection as it applies to claims 28, 29, 30 and 36 is moot and should be withdrawn.

The Examiner also contends that the specification provides insufficient written description for claims 37 and 44 (and thus dependent claims 41-43 and 45-46) directed to a fragment of the amino acid sequence of SEQ ID NO:1. Independent claims 37 and 44 (and thus dependent claims 41-43 and 45-46) have been amended to require that the polypeptide fragment is between 40 and 66 amino acids in length. Applicant submits that the claims as amended relate to a discrete number of possible peptide fragments and the specification sufficiently describes the use of these peptides to modulate an immune response. Thus, the rejection is overcome and should be withdrawn.

CLAIM REJECTIONS -- §102(b)

Claims 37-40 and 44 were rejected as anticipated by Banks *et al.* ("Banks"). Banks discloses polypeptides of 17 and 31 amino acids in length, which are fragments of SEQ ID NO:1. Claims 38-40 have been cancelled. Thus, this rejection is traversed to the extent that it applies to these claims. Claim 37 and 44 have been amended to recite fragments of SEQ ID NO:1 which are at least 40 amino acids in length.

Applicant notes that the test for anticipation, as well as infringement, of a claim is whether the claim reads on a reference or a potentially infringing method or article, not the reverse. In other words, everything recited in the claim must be found in the reference. As noted by the Federal Circuit, "Anticipation of a patent claim requires a finding that the claim at issue 'reads on' a prior art reference." Atlas Powder Co. v. IRECO, Inc., 51 USPQ 2d 1943, 1945 (Fed. Cir. 1999) (citations omitted).

Claims 37 and 44, as amended, recite a fragment of sequence SEQ ID NO:1 which is between 40 and 66 amino acids long. Therefore, in order for the claimed sequence to be anticipated by Banks, it must be possible to "read" the full-length sequences of the claim "on" the reference. In other words, the prior art reference must include a fragment of between 40 and 66 contiguous amino acids from SEQ ID NO:1. Banks does not disclose such a sequence. Thus, claims 37 and 44, as amended, are not anticipated by Banks.

CLAIM REJECTIONS – §103(a)

Claims 37 and 42-46 have been rejected as obvious over Banks, in view of U.S. Pat. No. 6,074,673 ("Guillen") or U.S. Pat. No. 5,965,709 ("Presta"). The Examiner contends that the invention claimed in claims 42 and 45 differs from Banks only by the recitation of the method further comprising administering one or more additional bee venom polypeptides. The Examiner also contends that the invention claimed in claims 43 and 46 differs from Banks only by the recitation of the method further comprising administering one or more additional bee venom polypeptides selected from phospholipase A_2, hyaluronidase, allergen C, mellitin, adolapin, minimine, protease inhibitor, acid phosphatase, and glycosylated IgE-binding proteins, or analogs or derivatives thereof.

However, the Examiner further notes that Guillen teaches a method of modulating an immune response comprising administering an allergy desensitization composition of polypeptides from bee venom, including phospholipase A2, hyaluronidase, mellitin, and polypeptides from bee venom.

Further the Examiner also notes that Presta teaches IgE antagonists which are analogs and derivatives of IgE binding protein for the treatment of allergic disease, and also teaches one to combine the antagonist with other known therapy. Therefore, according to the Examiner, "it is prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the polypeptide fragments from bee venom as taught by Banks *et al.* with the polypeptides from the bee venom . . .or the analog or derivatives of the IgE binding protein...for treatment of allergy." (Office Action at page 9).

In order to establish a *prima facie* case of obviousness, the combination of cited references must teach or suggest all of the limitations of the claimed invention. (*See* MPEP § 2143).

Here, Applicant has amended independent claims 37 and 44 to specify that the method of modulating an immune response comprising administering one or more polypeptides which are fragments of SEQ ID NO:1 between 40 and 66 amino acids in length. Banks, alone, or in combination with Guillen or Presta, does not teach or suggest such a fragment. As noted above, Banks discloses polypeptides of 17 and 31 amino acids in length which are fragments of SEQ ID

NO:1. The additional polypeptides disclosed by Guillen or Presta are bee venom polypeptides such as phospholipase A_2, hyaluronidase, allergen C, mellitin, adolapin, minimine, protease inhibitor, acid phosphatase, and glycosylated IgE-binding proteins, or analogs or derivatives thereof. These are not polypeptides of SEQ ID NO:1 or fragments thereof. Therefore the addition of Guillen or Presta does not cure the deficiencies of Banks.

Therefore, Applicant contends that pending claims 37 and 42-46 are not obvious over Banks in view of Guillen or Presta. Accordingly, Applicant respectfully requests that the rejection of these claims be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact either of the undersigned at the telephone number provided below.

Respectfully submitted,

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Appendix A

Version with Markings to Show Changes Made

In the Specification:

On page 4, the paragraph beginning at line 19 was amended as follows:

-- FIG. 1 is a schematic representation of the Api m 6 isoforms. The order of the amino acids in brackets was not determined. In this figure, Api m 6.01 refers to SEQ ID NO:1; Api m 6.02 refers to SEQ ID NO:2; Api m 6.03 refers to SEQ ID NO:3; Api m 6.04 refers to SEQ ID NO:4.--

On page 11, the paragraph beginning at line 19 was amended as follows:

-- Also included in the invention are fragments of a protein having a portion of the amino acid sequence of any of SEQ ID NOs:1-4. The fragment preferably has one or more of the herein described activities of an Api m 6 protein. The fragment can be, *e.g.*, 6-72, [20-90,]30-70, or 40-60 amino acids in length.--

On page 24, the second full paragraph beginning at line 19 was amended as follows:

-- In order to enhance stability and/or reactivity, peptides can also be modified to incorporate one or more polymorphisms in the amino acid sequence of a protein allergen resulting from natural allelic variation. Additionally, D-amino acids, non-natural amino acids or non-amino acid analogues can be substituted or added to produce a modified peptide within the scope of this invention. Furthermore, peptides can be modified to produce a peptide-PEG conjugate. Modifications of peptides can also include reduction/alkylation (Tarr in: *Methods of Protein Microcharacterization*, J.E. Silver, ed. Humana Press, Clifton, NJ, pp 155[—]-194 (1986)); acylation (Tarr, *supra*); esterification (Tarr, *supra*); chemical coupling to an appropriate carrier (Mishell and Shiigi, eds., [*Selected Methods*] *Selected Methods in Cellular Immunology*, WH Freeman, San Francisco, CA (1980); U.S. Patent 4,939,239); or mild formalin treatment (*Marsh International Archives of Allergy and Applied Immunology* 41: 199-215 (1971)).--

In the Claims:

28. (Twice Amended) A method of modulating an immune response, said method comprising administering a substantially pure polypeptide comprising [an] the amino acid sequence [at least 70% identical to the amino acid sequence] of SEQ ID NO:1 to a subject in need thereof in an amount sufficient to inhibit an immune reaction by the subject against said polypeptide.

30. (Twice Amended) The method of claim 29, wherein the second bee venom polypeptide is selected from the group consisting of phospholipase A_2, hyaluronidase, allergen C, mellitin, adolapin, minimine,[acid phosphatase,] protease inhibitor, [and]acid phosphatase, and glycosylated IgE-binding proteins, or analogs or derivatives thereof.

37. (Amended) A method of modulating an immune response, said method comprising administering a substantially pure polypeptide comprising a fragment of the amino acid sequence of SEQ ID NO:1 to a subject in need thereof in an amount sufficient to inhibit an immune reaction by the subject against said polypeptide, wherein the polypeptide is a fragment of between 40 and 66 amino acids in length.

38. Cancelled.

39. Cancelled.

40. Cancelled.

43. (Amended) The method of claim 42, wherein said one or more additional bee venom polypeptides are selected from the group consisting of phospholipase A_2, hyaluronidase, allergen C, mellitin, adolapin, minimine,[acid phosphatase,] protease inhibitor, [and]acid phosphatase, and glycosylated IgE-binding proteins, or analogs or derivatives thereof.

44. (Amended) A method of modulating an immune response, said method comprising administering one or more substantially pure polypeptides wherein said one or more polypeptides comprise fragments of the amino acid sequence of SEQ ID NO:1 to a subject in need thereof, in an amount sufficient to inhibit an immune reaction by the subject against said one or more polypeptides, wherein the polypeptide is a fragment of between 40 and 66 amino acids in length.

46. (Amended) The method of claim 45, wherein said one or more additional bee venom polypeptides are selected from the group consisting of phospholipase A_2, hyaluronidase, allergen C, mellitin, adolapin, minimine,[acid phosphatase,] protease inhibitor, [and]acid phosphatase, and glycosylated IgE-binding proteins, or analogs or derivatives thereof.